Clinical characteristics and risk of serious disease in patients referred to a diagnostic centre: a cohort study

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[1] Abbreviation: DCR: Danish Cancer Registry; GP: general practitioner; NPR: National Patient Registry

Abstract

Background: Little is known about the clinical characteristics of patients referred to a diagnostic centre through the Danish urgent referral pathway for non-specific serious symptoms. We aimed at estimating the distribution of serious disease and the diagnostic value of clinical characteristics for the diagnosis of cancer and serious non-malignant disease in these patients.

Method: A cohort study of 938 patients referred by their GP to the diagnostic centre at Silkeborg Regional Hospital. All patients were followed up for three months in national registries. The likelihood ratio (LR) of cancer or serious non-malignant disease were calculated in relation to clinical characteristics.

Results: A total of 327 (34.9%) patients were diagnosed with new serious disease within three months: 118 patients (12.6%) with malignant disease and 209 patients (22.3%) with non-malignant disease. Most patients presented general symptoms. The highest LR of cancer was found for abdominal mass, high lactate dehydrogenase or abnormal findings in the diagnostic imaging. The highest LR of non-malignant disease was found for swollen joints or abnormal auscultation of lung or chest.

Conclusions: Patients referred by their GP to the diagnostic centre have high risk of serious disease. A multidisciplinary diagnostic approach is needed to embrace the diagnostic spectrum.

Keywords: Early cancer diagnosis; neoplasm; urgent referral; Denmark; general practice

1. Introduction

An urgent referral pathway for non-specific serious symptoms was implemented in Denmark in 2011-2012 [1]. This pathway was part of the Danish three-legged cancer strategy and supplemented the urgent referral pathways, which were based on alarm symptoms for specific cancer types [2]. The aim was to expedite cancer diagnosis by providing new referral possibilities from general practice for patients with non-specific symptoms that could be signs of serious disease [3].

The implementation was supported by studies demonstrating that the urgent referral pathways favoured patients presenting with specific alarm symptoms of cancer, whereas patients not presenting with these specific alarm symptoms had increased diagnostic intervals [4,5]. A Danish study among general practitioners (GPs) showed that half of cancer patients presented with symptoms that could not be categorised as alarm symptoms at first presentation; they presented with either non-specific serious symptoms (20%) or vague symptoms (30%) [4].

To prevent long-lasting fragmented diagnostic pathways, the urgent pathway for non-specific serious symptoms was designed as a two-step approach [3]. First, the GP initiates the diagnostic workup on the basis of the imaging results and a standardised panel of blood tests ("triage function"). Second, if relevant, the patient is referred to the diagnostic centre, where a multidisciplinary team takes over the responsibility for the patient [6].

Non-specific symptoms do not have an obvious link to one certain disease type or organ system. Therefore, the referral criteria in the urgent referral pathway for non-specific serious symptoms are less definitive than the symptoms in the pathways for specific cancer types [1]. Thus, little is known about the clinical characteristics of patients referred to the diagnostic centre from the GP or about the diagnostic spectrum of serious disease and the role of the clinical characteristics in the diagnosis of serious disease among referred patients.

The aim of this study was to estimate the distribution of serious disease (cancer and serious non-malignant disease) and to describe and quantify the diagnostic value of the clinical characteristics for the diagnosis of serious disease among patients referred by their GP to the diagnostic centre at Silkeborg Regional Hospital.

2. Material and Methods

2.1 Study design

A prospective cohort study of patients aged 18 years or more referred by their GP to the diagnostic centre at Silkeborg Regional Hospital through the urgent referral pathway for non-specific serious symptoms between 1 July 2012 and 30 September 2014. Patients were followed up for three months in national registries for the diagnosis of new serious disease (cancer or serious non-malignant disease). We excluded patients referred to the diagnostic centre from a hospital department and patients who declined complete diagnostic workup.

2.2 Setting and organisation of diagnostic pathway

All Danish residents have free access to diagnostic services and treatment through the publicly funded health-care system. The Danish medical services are divided into five regions, and each of these regions has at least one diagnostic centre. Approximately 21 diagnostic centres have now been established in Denmark. Silkeborg Regional Hospital is situated in the Central Denmark Region, and the diagnostic centre has a catchment area of approx. 177,000 residents aged 18 years or older.

The triage function at Silkeborg Regional Hospital consists of imaging and a standardized blood test panel. The imaging includes a combined thoracic X-ray and ultrasound of the upper and lower abdomen. A CT scan of chest, abdomen and pelvis is performed if considered relevant by the radiologist. The results of the investigations are returned to the GP within three working days. The GP decides on further diagnostic steps within eight working days. If the triage function yields no obvious explanation for the patient's symptoms, the GP is advised to refer the patient to the diagnostic centre.

The diagnostic centre is run by specialists in internal medicine. All patients are assigned a personal coordinator during the diagnostic workup; the coordinator schedules visits for diagnostic investigations and keeps track of the outpatient diagnostic trajectory.

The first visit to the diagnostic centre is scheduled within 1-3 days after referral. Based on the medical history and the results of investigations, patients undergo individual diagnostic programmes; these are developed in a close cooperation between relevant experts, and all medical specialties are represented in the diagnostic centre. Furthermore, the diagnostic centre has made preferential arrangements with specialists to hasten the diagnostic investigations (e.g. gynaecological examination, endoscopy, diagnostic imaging and biopsy). The programme may include concurrent workup in different medical specialties (e.g. gastroenterology and gynaecology), and these are coordinated in the diagnostic centre. All medical specialties are available for consulting on daily multidisciplinary conferences. The diagnostic centre is responsible for the patient during the entire diagnostic workup, which must be completed within 16 calendar days.

2.3 Data

Eligible patients were included from a clinical database at the diagnostic centre at Silkeborg Regional Hospital. The data were consecutively recorded for each patient by the involved healthcare personal. We assigned the index date as the date of first visit at the diagnostic centre. The unique civil registration number assigned to all Danish residents at birth or immigration allowed linkage to national registries [7]. The clinical laboratory information system (LABKA) was used to retrieve information on results of blood tests performed within 14 days from the index date [8]. Included blood tests were part of the standardized blood test panel performed in the triage function, and test results were identified by unique codes in LABKA [9].

Patients were followed up for three months after index date for diagnosis of cancer in the Danish Cancer Registry (DCR) [10]. Patients with no registered malignant diagnosis in the DCR were followed up in the

National Patient Registry (NPR) for a non-malignant diagnosis [11]. Both registries were coded using the International Classification of Diseases, 10th edition (ICD-10). For each person, only the incident diagnosis was included; diagnoses registered within the ten years preceding the index date were excluded. Three authors (EN, UF and PV) reviewed all diagnoses and dichotomised into: 1) serious disease or 2) not serious disease. Disagreements were discussed until consensus was reached.

2.4 Variables

Symptoms were defined as presence or absence of 21 specified symptoms at the first visit to the diagnostic centre. Clinical findings were defined as findings by the physician during the clinical examination of the patient at the first visit to the diagnostic centre. Blood tests were defined as abnormal or normal for 15 specified routine blood tests according to the reference range established by the local department of clinical chemistry. Diagnostic imaging was defined as abnormal on the basis of the description by the radiologist if one of the following was found: 1) findings suspicious of malignancy or 2) non-malignant findings requiring treatment or further diagnostic workup.

2.5 Statistical analysis

The outcomes in the data analysis were: diagnosis of cancer or new serious non-malignant disease within three months after the index date. Categorical data were analysed as numbers and proportions. The likelihood ratio (LR) of cancer and the LR of serious non-malignant disease were calculated for presented symptoms, abnormal clinical findings, abnormal blood tests and diagnostic imaging. The 95% confidence intervals (95% CI) were calculated assuming exact binomial distribution. No alterations were made for missing data on presence/no presence of serious disease. The data analysis was conducted using Stata statistical software v. 14.

2.6 Ethical considerations

The study was approved by the Danish Data Protection Agency (ref. no. 2013-41-2232). According to Danish law, no approval was required from the Danish health research ethics committees for this type of study.

3. Results

3.1 Population

A total of 1356 patients aged 18 years or more were referred during the inclusion period. After exclusion of 384 (28.3%) internal referrals from hospital departments and 34 patients (2.5%) who declined complete diagnostic workup, the study population consisted of 938 patients. The median waiting time from referral to visit was one calendar day (interquartile range (IQI): 1-3 days) and the median time from first visit to last visit was eight calendar days (IQI: 1-14) (data not shown).

3.2 Patient characteristics

The majority of referred patients were aged 60-79 years, and 516 patients (55%) were female (Table 1). Two thirds had a normal performance status, and half of patients had one or more chronic diseases before referral. A total of 30% were active smokers, and 20% of patients reported to consume alcohol on a daily basis.

3.3 Diagnoses

A total of 327 (34.9%) patients were diagnosed with new serious disease: 118 patients (12.6%) were diagnosed with a malignant disease and 209 patients (22.3%) were diagnosed with a new serious non-malignant disease (Table 2). The diagnostic spectrum consisted of a mix of different disease groups. The most frequent malignant disorders were haematological, colorectal, kidney, lung and pancreatic cancers. The most common serious non-malignant diagnoses were rheumatic diseases, gastrointestinal diseases, endocrine disorders and infectious diseases (Appendix A).

3.4 Presented symptoms and clinical findings at first visit

The majority of patients presented with two or more symptoms at the first visit to the diagnostic centre (Appendix B). The diagnostic value of presenting symptoms is shown in Table 3. Most patients had one or more general symptoms; the most frequent were weight loss, fatigue, loss of appetite, pain and general malaise.

The LRs of cancer were highest in patients with a lump (LR = 3.2) and patients with general malaise (LR = 1.8). Presented symptoms had a weaker association with non-malignant disease. The LR of non-malignant disease was highest in patients with pain (LR=1.4) or fatigue (LR=1.3). The LRs of cancer and non-malignant disease increased only marginally with increasing number of presented symptoms at first visit (Appendix B).

Table 4 shows the diagnostic value of abnormal clinical findings. Patients with abnormal clinical findings had an increased LR of both cancer and non-malignant disease. Abdominal mass (LR = 8.4) and lymph nodes (LR = 3.0) had high LRs of cancer. Swollen or tender joints (LR = 5.6) were associated with the highest LRs of non-malignant disease.

3.5 Abnormal blood test results and abnormal diagnostic imaging

Table 5 shows the diagnostic value of abnormal blood tests. The three most common laboratory findings were high inflammatory markers, anaemia and hypoalbuminaemia. High lactate dehydrogenase showed the strongest association with cancer (LR = 2.3), but no association was found with the diagnosis of non-malignant disease (LR = 0.9). For the remaining blood tests, the LRs of cancer and of non-malignant disease ranged from 1.0 to 2.2.

Table 6 shows the diagnostic value of available imaging results at first visit to the diagnostic centre. Abnormal findings on all three imaging modalities showed an increased LR of cancer. The LR of cancer was highest in patients with abnormal findings on abdominal ultrasound (LR=3.6). The LR of cancer was also increased among patients referred to a supplementary CT scan by the radiologist (LR=1.8). If abnormal

findings were seen on the CT, the resulting post-test probability of being diagnosed with cancer was 27.9 (95% CI: 22.6; 33.7) compared to 3.9% (95% CI: 1.3; 8.9) if no abnormal findings were seen in the CT scan. **4. Discussion**

4.1 Main findings

Of patients referred to the diagnostic centre, 34% were diagnosed with a new serious disease. The diagnostic spectrum was broad and consisted of both malignant disease (12%) and serious non-malignant disease (22%). Patients presented with various symptoms at first visit, but the majority presented with one or more general symptoms. Abnormal laboratory findings were common, but most were unspecific to cancer or non-malignant disease. This shows that the symptom pattern in these patients vary considerably and that they present many different signs of potential disease.

4.2 Discussion of findings and comparison with existing literature

The risk of cancer among patients referred to the urgent referral for non-specific serious symptoms has been reported to be between 12% and 22% in previous studies [3,12,13]. A UK study found the risk of cancer to be 11% for patients referred to an urgent referral pathway for a specific cancer type [14]. Several factors may explain the high risk of cancer in our study. First, all patients were referred after a GP-based triage function. Secondly, referrals were based on the GPs' suspicion of serious disease, which has a relative high positive predictive value of cancer [3,15,16]. Finally, the positive predictive value of non-specific symptoms for cancer in primary care are of a magnitude corresponding to many specific alarm symptoms [16,17]. Still, the appropriate conversion rate of cancer among patients referred to the diagnostic centre must be examined in further studies.

Serious non-malignant diseases were frequent in our study, and they consisted of a wide variety of diagnoses within different medical specialities. The findings highlight the importance of taking a wide

diagnostic approach to patients referred with non-specific serious symptoms; this also includes providing easy access to relevant medical specialities at the diagnostic centres.

In primary care, general symptoms (such as unintended weight loss, fatigue or loss of appetite) are frequently seen among consulting patients who are later diagnosed with cancer [18,19]. However, these symptoms are also features of both self-limiting and serious non-malignant conditions. It may thus be difficult for the GP to identify the correct referral pathway for patients presenting with general symptoms. The clinical consequence is that the diagnosis of any serious disease may be delayed. For some cancer types, this can lead to poorer survival [20]. The diagnostic centre offers a fast-track evaluation to confirm or refute the suspicion of serious disease in the patients. However, further studies are needed to analyse the prognosis among patients referred to the diagnostic centres.

Patients suspected of malignancy on chest X-ray or abdominal ultrasound in the triage function were offered a direct CT scan of thorax, abdomen and pelvis. At other diagnostic centres, all patients are offered a CT scan of thorax, abdomen and pelvis in the triage function immediately after referral from the GP [12]. Our findings suggest that chest X-ray, abdominal ultrasound and CT scan may all be useful in the initial diagnostic approach. A potential disadvantage of an indiscriminate use of CT scans in patients with non-specific symptoms may be: 1) risk of radiation exposure, 2) higher resource allocation and 3) incidental findings and overdiagnosis. Still, the effect of different radiological strategies among patients referred with non-specific serious symptoms needs to be examined in further studies.

4.3 Strengths and limitations

The key strengths of this study are the prospective collection of data with nearly complete registration of all patients referred to the diagnostic centre. Furthermore, the information was systematically registered in the database by clinicians, and the included blood tests were all performed as part of a standardised panel, which reduced the risk of information bias. Additionally, the calculated likelihood ratios are not dependent on the prevalence of disease, which increases the generalisability of the results.

The register data are considered valid and complete as information in the DCR is registered continuously on the basis of national registries, and the records have been shown to be highly accurate [10]. The completeness in the NPR is high for serious non-malignant diseases as these should always lead to hospital activity [11]. The same applies for the LABKA system, which forms the basis of all clinical information on blood test results in the Central Denmark Region [8].

We used a follow-up period of three months as we wanted to include incident diagnoses that were associated with the diagnostic workup in the urgent referral for non-specific serious symptoms. We chose to exclude patients who declined complete diagnostic workup; this was done to avoid any information bias from incomplete registrations of diagnoses in the national registries for these patients. However, we were not able to confirm whether all new diagnoses of serious disease were associated with workup at the diagnostic centre.

We focused on calculating the diagnostic value of single clinical characteristics in the diagnosis of cancer and serious non-malignant disease as our aim was to describe the clinical characteristics in this previously undescribed group of patients. However, in clinical practice, diagnostic clues obtained from patient history, clinical examinations, blood tests and imaging results are often mutually dependent [21]. Further studies applying a multivariable approach are needed to analyse how the different clinical information available at first visit to the diagnostic centre may help the diagnostic workup in practice.

We included only patients referred from the GP, thereby reducing any selection bias introduced by internal referrals from other hospital departments. Still, our results are based on only a single centre, and the diagnostic spectrum may be different in other settings.

5. Conclusions

Patients referred by their GP to the diagnostic centre have a high risk of serious disease, and the diagnostic centre constitutes an initiative to support the GP in the difficult diagnostic workup when serious disease is

suspected. The diagnostic spectrum is wide among patients referred with non-specific serious symptoms, and patients presenting with non-specific serious symptoms in general practice may be at risk of experiencing multiple referrals to different medical specialities and a fragmented diagnostic pathway. The urgent referral pathway for non-specific serious symptoms enables the GP to refer patients to the diagnostic centre for a coherent and coordinated diagnostic trajectory.

At the diagnostic centre, a multidisciplinary diagnostic approach is needed to ensure that the wide spectrum of both malignant and benignant diseases is taken into account. It is a crucial feature that the diagnostic centres are organised with easy access to relevant investigations and different medical specialities.

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Table 1

Characteristics of patients investigated at the diagnostic centre (n = 938)

Variable	Number of patients (%)	
Gender		
Female	516	(55.0%)
Male	422	(45.0%)
Age group (yrs)		
18-39	47	(5.0%)
40-59	243	(25.9%)
60-79	546	(58.2%)
> 80	102	(10.9%)
WHO performance status[a]		
0	588	(65.9%)
1	198	(22.2%)
≥ 2	107	(12.0%)
Chronic diseases prior to referral[a]		
0	456	(51.1%)
1	142	(15.9%)
2	140	(15.7%)
≥ 3	155	(17.4%)
Type of chronic disease[a]		
Hypertension	208	(23.3%)
Osteoarthritis or inflammatory arthritis	110	(12.3%)
Earlier cancer (besides non melanoma skin cancer)	98	(11.0%)
Chronic obstructive lung disease	96	(10.8%)
Diabetes	82	(9.2%)
Ischemic heart disease	72	(8.1%)
Mental illness[b]	65	(7.3%)
Stroke	55	(6.2%)
Osteoporosis	49	(5.5%)
Smoking[a]		
Current smoker	263	(29.4%)
Former smoker/intermittent smoking	288	(32.3%)
Never smoked	342	(38.3%)
Drinking habits[a]		
Daily drinking	173	(19.4%)
No daily drinking	720	(80.6%)

[a] 893 number of valid responses.

[b] 41 patients had mild to medium mental illness, and 24 had moderate to severe mental illness.

Table 2

Type of serious disease among 118 patients diagnosed with cancer and 209 patients diagnosed with a non-malignant disease

Variable	Number of patients (%)	
Cancer		
Diagnosed with cancer within three months	118	(12.6%)
Cancer type		
Haematological cancer[a]	30	(25.4%)
Colorectal cancer	21	(17.8%)
Kidney cancer	12	(10.2%)
Lung cancer	11	(9.3%)
Pancreatic cancer	10	(8.5%)
Prostate cancer	8	(6.8%)
Ovarian cancer	7	(5.9%)
Upper gastro-intestinal cancer	6	(5.1%)
Breast cancer	4	(3.4%)
Primary site unknown	4	(3.4%)
Other specific cancer types[b]	5	(4.2%)
Non-malignant disease		
Diagnosed with serious non-malignant disease within three months	209	(22.3%)
Medical speciality of non-malignant disease[c]		
Rheumatology	54	(25.8%)
Gastroenterology	38	(18.2%)
Endocrinology	31	(14.8%)
Infectious diseases	28	(13.4%)
Haematology	19	(9.1%)
Respiratory medicine	18	(8.6%)
Vascular diseases	16	(7.7%)
Cardiology	14	(6.7%)
Nephrology	9	(4.3%)
Neurology	9	(4.3%)
Psychiatry	4	(1.9%)
Medical side effects	4	(1.9%)
Otorhinolaryngology	3	(1.4%)
Gynaecology and urology	3	(1.4%)

[a] Haematological cancers included 17 patients with lymphoma, 10 patients with malignant plasma cell disorders and 3 patients with leukaemia.

[b] Refers to cancer types diagnosed in three or less patients.

[c] Proportion of diagnoses is over 100% as 34 patients had a mix of different serious non-malignant diagnoses.

Table 3

Symptoms presented at first visit to the diagnostic centre and likelihood ratio (LR) of cancer and serious non-malignant diseases (n = 893)

Symptom	Patients with symptom (%)		LR of cancer (95% CI)		LR of non-malignant disease (95% CI)	
General symptoms						
Any general symptom	763	(85.4%)	1.0	(0.9;1.1)	1.1	(1.0; 1.1)
Weight loss[a]	472	(52.9%)	1.0	(0.8; 1.2)	1.0	(0.9; 1.2)
Fatigue	437	(48.9%)	1.1	(0.9; 1.4)	1.3	(1.1;1.5)
Loss of appetite or nausea	323	(36.2%)	1.3	(1.0; 1.6)	0.9	(0.7; 1.1)
Pain[b]	256	(28.7%)	1.2	(0.9; 1.6)	1.4	(1.1; 1.7)
General malaise	231	(25.9%)	1.8	(1.4; 2.3)	1.0	(0.8; 1.3)
Night sweats	175	(19.6%)	1.1	(0.8; 1.6)	0.9	(0.6; 1.2)
Fever	58	(6.5%)	1.0	(0.5; 2.1)	1.4	(0.8; 2.5)
Focal symptoms						
Any focal symptom	517	(57.9%)	1.2	(1.0; 1.3)	1.1	(1.0; 1.2)
Lung symptoms						
Any lung symptom	229	(25.6%)	1.1	(0.8; 1.6)	1.2	(1.0; 1.6)
Shortness of breath	157	(17.6%)	1.4	(1.0; 2.0)	1.2	(0.9;1.7)
Cough	136	(15.2%)	0.9	(0.6; 1.5)	1.3	(0.9; 1.8)
Haemoptysis	9	(1.0%)	0.9	(0.1; 6.9)	0.0	n/a
Digestive symptoms						
Any digestive symptom	202	(22.6%)	1.2	(0.8; 1.6)	1.0	(0.7; 1.3)
Change of bowel habits	164	(18.4%)	1.3	(0.9; 1.8)	0.8	(0.6; 1.2)
Dysphagia	39	(4.4%)	1.0	(0.4; 2.6)	1.7	(0.9; 3.3)
Blood in stool	37	(4.1%)	0.6	(0.2; 2.0)	0.7	(0.3; 1.6)
Urological symptoms						
Any urological symptom	77	(8.6%)	2.0	(1.2;3.3)	1.4	(0.9;2.2)
Difficulty urinating	66	(7.4%)	1.7	(1.0; 3.0)	1.3	(0.8; 2.2)
Blood in urine	17	(1.9%)	2.9	(1.0; 8.1)	1.1	(0.4; 3.2)
Other symptoms						
Vertigo	148	(16.6%)	1.5	(1.0; 2.2)	1.2	(0.9; 1.7)
Headache	84	(9.4%)	0.5	(0.2; 1.1)	1.0	(0.6; 1.6)
Lump	57	(6.4%)	3.2	(1.9; 5.4)	0.3	(0.1; 0.8)
Abnormal vaginal bleeding[c]	11	(1.2%)	0.0	n/a	1.2	(0.3; 4.4)
Change in mole or sores that do not heal	10	(1.1%)	0.8	(0.1;6.1)	2.3	(0.7; 8.1)

[a] Weight loss within the last two months.

[b] Pain could be both generalised and localised.

[c] Abnormal vaginal bleeding among 495 women.

Table 4

Abnormal clinical finding at first visit to the diagnostic centre and likelihood ratio (LR) of cancer and serious non-malignant disease (n = 893)

Clinical finding	Number of patients (%)		LR of cancer (95%CI)		LR of non-malignant disease (95%CI)	
Any abnormal clinical finding						
Yes	267	(29.9%)	1.9	(1.6 ;2.4)	1.6	(1.3; 1.9)
No	626	(70.1%)	0.7	(0.5; 0.8)	0.8	(0.7; 0.9)
Type of abnormal clinical finding						
Abdomen*	116	(13.0%)	3.0	(2.2; 4.3)	1.4	(1.0; 2.1)
Abdominal tenderness[a]	34	(3.9%)	1.8	(0.8; 4.1)	1.9	(0.9; 3.7)
Abdominal mass[a]	33	(3.7%)	8.4	(4.4; 16.2)	0.5	(0.2; 1.3)
Musculoskeletal	60	(6.7%)	0.8	(0.3; 1.7)	3.7	(2.3; 6.0)
Swollen or tender joints[b]	13	(1.5%)	0.6	(0.1; 4.4)	5.6	(1.8; 16.8)
Lymph node	47	(5.3%)	3.0	(1.6; 5.4)	0.5	(0.2; 1.2)
Chest**	43	(4.8%)	0.9	(0.4; 2.3)	2.0	(1.1; 3.7)
Skin	39	(4.4%)	1.5	(0.7; 3.4)	1.9	(1.0; 3.6)
Breast[c]	24	(4.9%)	1.1	(0.3; 3.5)	0.5	(0.2; 1.7)
Neurology	18	(2.0%)	0.9	(0.2; 3.7)	2.2	(0.9; 5.6)

* Abnormal findings in examination of abdomen or rectal digital examination.

**Abnormal auscultation of lung or heart.

[a] 882 valid registrations, [b] 890 valid registrations, [c] among 495 women.

Table 5

Abnormal blood test results and likelihood ratio (LR) of cancer and serious non-malignant disease

Test	Number of patients with valid tests	Number of patients with abnormal tests (%)		LR of cancer (95% CI)		LR of non-malignant disease (95% CI)	
Haematology							
Low haemoglobin	873	305	(34.9%)	1.5	(1.2; 1.8)	1.6	(1.4; 2.0)
High platelet count	873	157	(18.0%)	1.8	(1.3; 2.6)	1.7	(1.3; 2.3)
High white blood cell count	873	119	(13.6%)	1.3	(0.9; 2.0)	1.5	(1.1; 2.1)
≥ 2 abnormal tests of the above	866	138	(15.9%)	1.9	(1.4; 2.7)	2.0	(1.5; 2.7)
Inflammatory markers							
High ESR	808	283	(35.0%)	1.6	(1.3; 2.0)	1.6	(1.3; 1.9)
High CRP	864	272	(31.5%)	1.9	(1.6; 2.3)	1.7	(1.4; 2.0)
2 abnormal test results	794	193	(24.3%)	1.7	(1.3; 2.2)	2.0	(1.6; 2.4)
Liver function tests							
Low albumin	874	210	(24.0%)	2.1	(1.6; 2.7)	1.5	(1.2; 1.9)
High alkaline phosphatase	862	159	(18.4%)	1.9	(1.4; 2.6)	1.2	(0.8; 1.6)
High ALK	863	66	(7.6%)	1.5	(0.8; 2.6)	1.4	(0.9; 2.4)
High bilirubin	861	19	(2.2%)	2.3	(0.9; 6.3)	1.0	(0.3; 2.8)
≥ 2 abnormal test results	857	105	(12.3%)	2.2	(1.5; 3.3)	1.6	(1.1; 2.4)
Metabolic tests							
High lactate dehydrogenase	838	100	(11.9%)	2.3	(1.5; 3.4)	0.9	(0.6; 1.4)
High calcium	820	65	(7.9%)	1.6	(0.9; 2.9)	1.2	(0.7; 2.0)
2 abnormal test results	796	7	(0.9%)	2.6	(0.5; 13.0)	1.5	(0.4; 5.5)

Abbreviations: ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; ALK = Alanine amino-transaminase.

Table 6

Available imaging for clinical assessment at first visit to the diagnostic centre and likelihood ratio (LR) of cancer and serious non-malignant disease

Imaging	Number of patients (%)		LR of cancer (95% CI)		LR of non-malignant disease (95% CI)	
Chest X-ray[a]						
Abnormal findings on chest X-ray	113	(14.0%)	1.8	(1.2; 2.7)	1.7	(1.2; 2.5)
No abnormal findings on chest X-ray	696	(86.0%)	0.9	(0.8; 1.0)	0.9	(0.8; 1.0)
Abdominal ultrasound[b]						
Abnormal findings on ultrasound	155	(18.8%)	3.6	(2.8; 4.7)	0.9	(0.6; 1.2)
No abnormal findings on ultrasound	600	(72.6%)	0.5	(0.4; 0.7)	1.0	(0.9; 1.1)
Inconclusive ultrasound examination	71	(8.6%)	1.1	(0.6; 2.1)	1.1	(0.7; 1.9)
Supplementary CT scan performed[c]*						
Yes	404	(45.2%)	1.8	(1.6; 2.1)	1.2	(1.0; 1.4)
No	489	(54.8%)	0.4	(0.3; 0.6)	0.9	(0.7; 1.0)
Results of CT scan[d]**						
Abnormal findings on CT scan	265	(67.6%)	1.5	(1.4; 1.7)	1.1	(0.9; 1.2)
Normal findings on CT scan	127	(32.4%)	0.2	(0.1;0.4)	1.0	(0.7; 1.3)

*The radiologist decided whether a supplementary CT scan of thorax, abdomen and pelvis was needed based on results from chest X-ray and abdominal ultrasound.

** The likelihood ratio among patients referred to CT scan by the radiologist.

[a] 809 valid registrations, [b] 826 valid registrations, [c] 893 valid registrations, [d] 392 valid registration.

Appendix A.

Overview of diagnosed serious non-malignant diseases in the four most common medical specialities

Variable	Number of patients (%)	
Rheumatology (n = 54)		
Polymyalgia rheumatic and giant cell arteritis	25	(46.3%)
Inflammatory arthritis	17	(31.5%)
Sarcoidosis	7	(13.0%)
Osteoporosis with pathological fractures	5	(9.2%)
Gastroenterology (n = 38)		
Gastrointestinal tract disease	21	(55.3%)
Liver and biliary disease	9	(23.7%)
Pancreatic disease	8	(23.0%)
Endocrinology (n = 31)		
Thyroid disease	15	(48.4%)
Diabetes mellitus	5	(16.1%)
Other endocrinological diseases	11	(35.5%)
Infectious diseases (n = 28)		
Pneumonia	11	(39.3%)
Other infectious diseases	17	(60.7%)

Appendix B.

Number of symptoms registered at first visit to the diagnostic centre and likelihood ratio (LR) of cancer and non-malignant disease (n = 893)

Number of symptoms	Number of patients with symptom (%)		LR of cancer (95% CI)		LR of non-malignant disease (95% CI)	
All symptoms[a]						
0	77	(8.6%)	0.8	(0.5; 1.3)	0.8	(0.5; 1.1)
1	157	(17.6%)	0.8	(0.5; 1.3)	0.8	(0.5; 1.1)
2-3	303	(33.9%)	0.8	(0.6; 1.1)	1.0	(0.8; 1.3)
≥ 4	356	(39.9%)	1.3	(1.1; 1.6)	1.2	(1.0; 1.4)
General symptoms[b]						
0	130	(14.6%)	1.0	(0.6; 1.6)	0.6	(0.4; 1.0)
1	217	(24.3%)	0.8	(0.6; 1.2)	1.0	(0.8; 1.1)
2-3	362	(40.5%)	0.9	(0.7; 1.1)	1.0	(0.9; 1.3)
≥4	184	(20.6%)	1.4	(1.1; 1.9)	1.3	(1.0; 1.6)
Focal symptoms[c]						
0	376	(42.1%)	0.8	(0.6; 1.1)	0.9	(0.7; 1.1)
1	274	(30.7%)	0.9	(0.7; 1.3)	1.1	(0.9; 1.4)
2-3	196	(22.0%)	1.4	(1.0; 1.9)	1.2	(0.9; 1.5)
≥ 4	47	(5.3%)	1.4	(0.7; 3.0)	0.9	(0.5; 1.8)

[a] The 21 different symptoms are shown in table 3 in the article.

[b] Fatigue, fever, general malaise, loss of appetite, night sweats, pain and weight loss.

[c] Blood in stool, blood in urine, change of bowel habits, cough, difficulty urinating, dysphagia, haemoptysis, headache, lump, shortness of breath and vertigo.